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RESULTS OF THE BITERMINAL TRANSPLANTATION OF VEINS.

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THE first series of experiments performed demonstrated that by interposing between the two cut ends of an artery a segment of vein it is possible to restore quickly the arterial circulation, and that the venous segment is able to perform the principal arterial functions. A summary of the immediate results of this operation, together with the main conclusions to be drawn therefrom, have already been published.[1]

After finding that a venous segment transplanted on the arterial apparatus adequately supported the blood pressure, we tried to determine to what extent such a segment would acquire arterial characters. It is well known, indeed, that the function and development of an organ are intimately associated, and that even in adult animals an organ or tissue may be caused to undergo extensive anatomical and physiological development. It might be assumed, therefore, that a vein acquiring the functions of an artery would become arterial in all its characters. But as we believe this method of transplanting veins may be used in man, as in the treatment of large wounds of arteries and aneurysms, we consider it necessary to determine carefully the permanent effects of the arterial blood pressure on the venous wall, before this application is made.

A second series of experiments was performed. Three dogs were operated on under aseptic technique. Two of the animals were etherized and the results of the operations studied six and fourteen days respectively after the operation. The third animal was kept alive. By examining it over a long period of time it may be possible to determine the permanent results of the operation.[2]

Experiment I. Transplantation was made of a segment of the femoral vein between the two cut ends of the femoral artery. The ends of the venous segment were dissected and transplanted on the artery, but all the middle portion was permitted to retain its normal connections, including its collaterals. After the circulation was re-established these collaterals became similar to small collateral arteries. It was therefore an incomplete biterminal transplantation.

Experiment II. Complete biterminal transplantation was made. A long segment of the external jugular vein was dissected out and completely extirpated and put in a glass of isotonic sodium chloride solution. Afterward the carotid artery was dissected and severed. The venous segment was interposed between and united to its cut ends, and the circulation re-established.

Experiment III. Same as Experiment II.

Physiological Results. Immediately after the re-establishment of the circulation in an artery after the interposition of a segment of vein in its course the circulation through the portion of the artery peripheral to the venous segment is somewhat modified, the pulsations being weaker. In a case of interposition of a very long segment of the jugular vein, between the cut ends of the carotid

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[1] Anastomosis and Transplantation of Bloodvessels, Amer. Med., 1905, vol. x, 284, 1101.

[2] This paper has been delayed in transmission. Since it was written numerous vascular transplantations have been performed. These operations have shown that the arteriovenous anastomoses remain in excellent condition twelve months after the operation, and that the modifications of the venous wall are constant and proportional to the increase of blood pressure. All the subsequent observations have confirmed the results given in this paper.

artery with excellent restoration of circulation, the pulsations of the artery distal to the segment were almost imperceptible to the touch, while between the segment and the heart the pulsations were strong. Manometric tracings of the arterial blood pressure and pulse central and distal to the venous segment showed marked differences in the case of the pulse, the distal tracings being the weaker, while the blood pressure was the same in both cases. This effect on the pulse was probably due to the semicircular shape the segment assumed, owing to its great length compared to the length of the interval it occupied between the ends of the artery. These observations were made about two hours after the operation. In order to ascertain what changes, if any, take place in the circulation longer intervals after the operation, the animals aseptically operated upon are being studied.

The first dog was examined the fifth and sixth days after the operation. The pulsations of the distal end of the femoral artery remained weaker than the pulsations of the corresponding point of the femoral artery of the other limb.

The second dog was examined the fifth, the thirteenth, and the fourteenth days after the operation. On the fifth day the pulsations were markedly weaker distal to the venous segment than between it and the heart, but on the thirteenth and the fourteenth days no difference in the pulsations on the two portions of the artery could be detected by a clinical examination. Immediately after this examination the animal was etherized and the artery exposed and dissected from the surrounding tissues. Direct examination confirmed the results of the clinical or external examination regarding the similarity of the arterial pulse above and below the venous segment.

Blood pressure and pulse tracings taken from the artery distal and central to the segment and recorded by a mercury manometer revealed no difference in the former and only slight differences in the latter.

It may, therefore, be concluded that the physiological differences in character of the arterial circulation distal and central to the venous segment present immediately after the operation are soon modified. This indicates the occurrence of adaptive anatomical changes in the segment.

On the third dog, the pulsations of the venous segment were easily detected by palpation and its wall seemed greatly thickened.[1]

ANATOMICAL RESULTS. *Macroscopic Examination.* The anatomical changes in the wall of the venous segment probably begin very soon after the operation, but for some days they cannot be detected macroscopically. On the sixth day the venous wall

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[1] At the present time, eight months after the operation, this dog is in excellent health, and the circulation is very active through the venous segment, which to the touch exhibits the characteristics of the carotid artery.

appeared normal in size and structure. By palpation no thickening of the wall could be detected. It had altered in hue, having become almost as white as the wall of the femoral artery. The distal anastomosis only was studied. The line of suturing was still easily seen. The union appeared to be directly between the ends of the vessels. A longitudinal incision was made through the wall of the venous segment, the distal anastomosis, and the wall of the artery for some distance in order to expose the endothelium and different coats of the vessel. The endothelium appeared normal and the point of anastomosis smooth and regular. The line of union was not visible, being concealed by an extremely thin flesh-colored ring. This appeared to be a sheath of organized fibrin of about the thickness of a thin cigarette paper and about 1 millimeter wide, excepting at one point, where it was almost 2 millimeters in width. In order to determine the cause of this inequality, a portion of the ring was carefully removed with the point of a scalpel. Then it was seen that the endothelium of the vessels was not perfectly approximated at the point of greatest width of the ring and that the intervening gap was filled with fibrin. The ring of fibrin was so thin and so tightly adherent to the wall of the vessel that thrombosis or other hindrance of any consequence to the circulation was not to be feared.

The probable explanation of the deposit of fibrin, on the basis of Morowitz's work on the coagulation of the blood, is that at the line of union of the cut ends of the vessels more or less thrombokinase, the amount depending on the degree of perfection of the approximation of the intimas, came in contact with the blood, and with calcium reacted with thrombogen, and thrombin was formed. This in turn acting upon the fibrinogen produced fibrin, which, owing to the comparative roughness of the interior of the bloodvessel at the line of anastomosis was then deposited as a ring. The size of this ring at any given point was directly proportional to the amount of coagulation, which in turn depended upon the amount of thrombokinase present. This fibrinous ring probably served a dual purpose: (*a*) by limiting the entrance and escape of thrombokinase into the circulation, thus rendering extensive intravascular coagulation improbable, and (*b*) by preventing hemorrhage into the surrounding tissues or into or between the coats of the vessels.

The dog examined fourteen days after the operation showed more profound changes in the character of the bloodvessel than the one examined on the sixth day. The appearance and the structure of the venous segment was greatly altered.

The segment appeared as a dilated portion of the carotid artery, which tapered abruptly at both ends, there being only a very slight thickening of the artery at the point of anastomosis. The line of union was concealed by a thin sheath of connective tissue. The external diameter of the venous segment was about twice as great as that of the artery. In hue it appeared the same as the artery. Surrounding it was a sheath of loose connective tissue similar to the external sheath of the artery. As the sheath was not adherent to the surrounding tissues the dissection of the segment was not more difficult than that of the artery.

The lumen of the venous segment and of the artery was exposed by a longitudinal incision through the walls. The diameter of the lumen of the venous segment was greater than that of the artery, but it was less than at the time of the operation. Near the points of anastomosis the diameter of the lumen of the venous segment became less than in the middle portion. A few longitudinal folds of the intima were observed. The endothelium was apparently normal, being white and glistening. The lines of union of the blood-vessels were covered by sound endothelium. The union appeared complete excepting possibly at one small point where a minute patch of fibrin was very tightly adhered to the wall of the venous segment. It was entirely confined to this small area, and when later examined microscopically it was seen to be organized and apparently being absorbed. It occurred at the anastomosis next the heart.

After being cut, the segment remained open like an artery. The macroscopic examination of the wall revealed great changes. It appeared almost three times as thick as the wall of the artery, and to be composed of an external and an internal part. The two parts were strongly united but they could be separated by careful dissection. The internal part had the appearance of an arterial wall, its tissues on section being very light in color and very dense. The external part of the wall was almost four times as thick as the internal. Its tissue was darker and less dense than that of the internal part. It appeared to consist of connective tissue.

Microscopic Examination. After finishing the macroscopic examination a longitudinal strip was removed from the lower end of the specimen, the incision being carried through the deposit of fibrin. The strip was two centimeters long; about one-fourth of its length consisted of artery and the remainder of the venous segment, the two being united at the point of anastomosis. After being fixed, embedded, cut, stained, and mounted, it was examined. Owing to the lack of time, only the hematoxylin-eosin stain and Unna's orcein stain for elastic fibers were used, and the examination was principally with a view to determine the relative thickness of the wall at different points and what coats were involved. In addition, all conditions observed that were considered of interest, are included in the description. Unfortunately the normal jugular vein removed from the animal was lost. So no absolute statements as to the increase in thickness of the wall can be made, but assuming that normally it was one-third the thickness of the carotid artery, which is a conservative assumption, the changes are enormous. For our present purposes, absolute measurements are unimportant, only *progressive or regressive* changes, *relative dimensions* and *tissues involved* in the changes being considered the points essential to determine.

Arterial Part. Beginning at the portion of the artery appearing in the specimen farthest from the point of anastomosis, the wall was 0.71 mm. thick and normal. The thickness and structure remained the same until a point about 5 mm. from the point of anastomosis was reached. Then the thickness began gradually to increase until at the point of anastomosis it was 1.19 mm. From this point back to the point where the thickening began, a wedge-shaped layer of granular material, in which were embedded scattering cells and fibers, was present between the middle and outer coat of the vessel. This largely accounts for the increase in thickness, the base of the layer of granular material being about 0.45 mm. wide.

The intima of the artery appeared normal. At the point of union with the venous segment it was bent outward with the middle coat toward the adventitia and appeared to form an anatomical union with the intima of the venous segment which was similarly bent. It was difficult to detect the exact relation of the intimas to each other, owing to the highly organized patch of fibrin present at the point of union.

The tunica media of the artery appeared to consist of an inner portion 0.28 mm. thick, composed of muscle fibers and elastic tissues, and an outer portion 0.09 mm. thick, mainly consisting of densely arranged elastic fibers, the total diameter of the coat being 0.37 mm. The reason for considering the outer layer of elastic tissue as a part of the middle coat is that the separation of the coats caused by the layer of granular material before mentioned occurred between this and the outer layers. Possibly it represents the layer sometimes described as the tunica elastica externa of Henle. The muscular layer ended near the point of anastomosis, by losing its muscular fibers, the elastic fibers becoming very densely packed and ending in a whorl around the silken ligature present in the end of the artery. The coat of fibrous tissue just external to the muscular coat also sent some fibers to join the whorl about the ligature, but for the most part the fibers ended abruptly. The corresponding coats of the wall of the venous segment ended very similarly around the ligature in its end, and the two whorls of fibers thus formed were connected by a well-developed band of fibers, which appeared to be continuous with the fibers in the inner portion of the muscular layer of the artery.

The tunica adventitia composing the remainder of the thickness of the arterial wall consisted mainly of connective-tissue fibers. In a zone near the outer margin of the coat, the fibers appeared denser, and among them were intermingled some elongated cells having large nuclei. In the region of the anastomosis this layer became very prominent, the fibers much denser, and the nuclei more numerous. It was continuous with a similar layer in the outer coat of the venous segment.

These results confirmed the conclusion based on the macroscopic examination that the wall of the artery was practically unaltered, excepting immediately at the point of anastomosis.

Venous Part. At the point of anastomosis the wall of the venous segment was approximately of the same thickness as the wall of the artery. From this point it very gradually increased in thickness for about 1.7 mm., at which point it was 1.57 mm. thick, which is slightly more than the thickness of the normal arterial wall. From this point it increased in thickness until a point about 6.0 mm. from the anastomosis was reached, where it was 2.88 mm. thick. From this point to the end of the specimen the wall was practically uniformly of this thickness.

The intima appeared uniform, being very similar to that of the artery in thickness. In the region of the anastomosis it was beneath the patch of fibrin and appeared to terminate, as before described, by uniting with the intima of the artery. The patch of fibrin measured 2.45 mm. in the longitudinal direction of the vessel and 0.48 mm. in thickness at the thickest point, which was near the point of anastomosis. It tapered gradually to a point at the other end. It appeared to be highly organized, consisting of a mass of cells which a band of fibers, about 0.22 mm. broad, and mainly from the muscular layer of the middle coat of the artery and vein, penetrated for some distance. The presence of these fibers rendered a definite statement as to whether or not the two intimas were directly united impossible, as they occurred at the point where the inner coats came the nearest together. In the centre of the organized mass an area 0.22 mm. by 0.64 mm., composed mainly of what appeared to be homogeneous blood pigment, occurred. This was the only sign of retrogressive change that could be detected. The free surface of the mass was absolutely smooth and regular.

The tunica media of the segment appeared to consist of two layers: an inner composed of muscle cells and longitudinal elastic fibers, and an outer consisting mainly of coarse, longitudinal, white connective and elastic fibers. In neither case were these layers as dense as the corresponding layers in the artery. At the point 1.7 mm. from the anastomosis the muscular layer was about 0.11 mm. thick and the fibrous layer 0.54 mm. At a point about 11 mm. from the anastomosis the former was 0.21 mm. and the latter 0.48 mm. At the anastomosis the muscular layer terminated mainly by sending elastic fibers to intermingle with similar fibers of the muscular coat of the artery, the muscle cells gradually disappearing. The fibers of the outer layer formed a dense whorl around the ligature situated at the end of the vein.

The adventitia also appeared to consist of two layers. At a point 1.7 mm. from the anastomosis the inner was 0.45 mm. and the outer ones 0.47 mm. thick, while 11.0 mm. from the anastomosis, they were 1.74 mm. and 0.46 mm. respectively. The outer layer was composed principally of loose connective tissue, which was continuous with the corresponding layer of the artery. The inner layer was continuous with the outer portion of the granular mass lying between the middle and outer coats of the artery, from which it differed markedly in structure, being mainly composed in the vicinity of the anastomosis of dense fibrous tissue containing many elongated nuclei. In addition it received fibers from the inner portion of the outer arterial coat; a few scattered elastic fibers were also present.

The ligatures 0.16 mm. in diameter and three in number were all situated between the middle and the outer coats. One situated in the end of the venous segment near the anastomosis and cut transversely was surrounded by elastic fibers, which were continuous with the fibers of the fibrous layer of the middle coat of the vein. Another cut in a similar manner and situated in the end of the artery was surrounded by fibers similar to the ones surrounding the first and were continuous with the fibers of the muscular layer of the artery. The other ligature was apparently cut through a knot. It was situated between the middle and outer arterial coats and was embedded in the base of the wedge of granular material occupying that situation. It may be that the wide separation of the coats of the vessel and the presence of such a large amount of granular material at this point was partially due to the presence of this knot, as it was quite bulky.

From the microscopic examination it is possible to conclude: (1) The wall of the artery is only slightly altered; (2) the wall of the vein has become enormously thickened, the muscular and fibrous layers of the middle coat and the inner layer of the outer coat being principally involved; (3) no evidence of weakening or breaking down of the wall is observed; and (4) the ligatures are enveloped in a dense coat of fibrous tissue.

CONCLUSIONS. 1. A venous segment interposed between the cut ends of an artery quickly undergoes anatomical changes.

2. From macroscopic and microscopic standpoints the vein has a strong tendency to assume the character of an artery.

3. From a physiological standpoint it performs the arterial functions.